Provisional Rejection of Claims 1-4, 6-9, 11, 12, 23-26, 50-53 and 56-58 For Obviousness-Type Double Patenting

Claims 1-4, 6-9, 11, 12, 23-26, 50-53 and 56-58 have been rejected under the judicially created doctrine of obviousness-type double patenting. The recited claims are said to be unpatentable over Claims 4-12 of copending Application No. 09/344,783.

A Terminal Disclaimer is being filed herewith.

Rejection of Claims 1-12, 23-27, 50-54 and 56-58 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-12, 23-27, 50-54 and 56-58 have been rejected under 35 U.S.C. § 112, second paragraph, as it is said they are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 23-27, 50-54 and 56-58 are said to be vague and indefinite "in that the metes and bounds of the terms 'regulable' gene and 'regulating expression' are unclear."

The terms in question have clear meanings understood by one of ordinary skill in the art. See page 25, line 20 to page 26, line 4, and page 29, lines 15-26. From this discussion, and from the "regulating" steps in the claims (for instance, step b) in Claim 1, step c) in Claim 6, step b) in Claim 7, etc.), it is apparent that the property of being "regulable" allows for the manipulation by the operator of an inducible or repressible gene.

Claims 1 and 6 are said to be vague and indefinite in that the metes and bounds of the phrase "monitoring said cell in the animal for a phenotypic effect" are said to be unclear.

Claims 1 and 6 have been amended to clarify their meaning. See Claims 56-58, page 7, lines 15-23, page 29, line 27 to page 30, line 10 for support for the amendments.

Claims 1 and 6 are said to be incomplete for omitting essential steps. The Examiner suggests that the omitted steps are a comparison to a control wherein cells of the same type, but not expressing the biomolecule, are introduced into the same kind of animal and observed for phenotypic effect (e.g. before and after induction of biomolecule expression).

Claims 1 and 6 have been amended to include the steps implied in the claims, as the Examiner suggested.

Claims 7, 8, 10-12, and 56-58 are said to be vague and indefinite in that the claims specify "suitable" control animals or cells. The Examiner states that "the term 'suitable' is inherently indefinite, in that the criteria for a 'suitable' control is likely to vary from investigator to investigator."

It is known from general scientific methods of experimentation, taught in every science course, that to conduct an experiment, one must designate a variable to test. In the test, the variable is changed; in the control, the variable remains constant. One of ordinary skill in the art would know what a "suitable" control is in the methods recited in the claims in question.

Examples of suitable control animals are illustrated in Example 3 on pages 42-44. See especially Table 3 on page 44, in which groups 6, 7 and 8 are control groups of animals for test groups 2, 3 and 4, respectively, and group 1 is a further control group. All of the control groups are suitable controls which can be used for comparison with the test groups for determining the effect of induction of the production of Pro-3 peptide by anhydrotetracycline. One of ordinary skill in the art, studying these examples, and considering his or her own knowledge and experience in designing experiments, would have no difficulty understanding what a suitable control animal is.

Examples of suitable control cells are illustrated in Example 2. See especially page 41, line 20 to page 42, line 2, and Figures 3A and 3B. The *E. coli* strain bearing the Pro-3 expression vector was cultured with the addition of, or without the addition of, anhydrotetracycline. The *E. coli* strain bearing the GST vector was cultured in the same manner as the test strain bearing the plasmid encoding the Pro-3 peptide, and anhydrotetracycline was added or not added to portions of the culture. One of ordinary skill in the art would understand that the *E. coli* strain bearing the Pro-3 expression vector to which anhydrotetracycline was not added, and the *E. coli* strain bearing the GST (parental type) vector, with or without the addition of anhydrotetracycline, would be suitable controls in this case. One of ordinary skill in the art would be able to follow this example, and to devise other suitable control strains, following this example and using his or her own knowledge of the principles of experimental design.

Claim 7 is said to be vague and indefinite "in that there is no clear and positive prior antecedent basis for the terms 'fewer cells,' 'number of cells,' and 'growth of cells' in step (c) of

the claim. Claim 8 is said to be vague and indefinite "in that there is no clear and positive prior antecedent basis for the term 'of growth of cells' in step (d) of the claim."

Claims 7 and 8 have been amended as the Examiner has suggested.

Claim 11 is said to be vague and indefinite "in that the metes and bounds of the term 'normal' growth are unclear."

Claim 11 has been amended to not use the term *normal*.

Claim 11 is said to be vague and indefinite for the phrase ". . . then the biomolecule is a biomolecular inhibitor of growth."

Claim 11 has been amended to clarify the meaning of the phrase.

Claim 23 is said to be incomplete for omitting essential steps. More specifically, the Examiner states that the omitted step is a step wherein the effects of the compound on the cell with regard to phenotypic effect are confirmed.

Claim 23 has been amended so that the conclusion agrees with the preamble. See page 32, lines 19-20 for support for the amendment.

Claim 50 is said to be vague and indefinite "in that there is no clear and positive antecedent basis for the term 'the biomolecule' in step (d) of the claim." It is also said that the end result of the claim does not match the preamble, and that there appears to be a missing step of confirming that a test compound has the same phenotypic effect on the target cell as the biomolecular binder.

Claim 50 has been amended so that the terms have proper antecedent basis, and so that the result of the claim matches the preamble, without any missing steps.

Claims 56-58 are said to be incomplete for omitting an essential step, wherein the essential step is infection of the control animals with the cells.

Claims 56-58 have been amended to include the step implied by further steps of the method, that of infecting control animals with a form of the pathogen used to infect the test strain.

Claims 56 and 57 are said to be incomplete for omitting an essential step, the step being "confirmation that a test compound which binds competitively to a target cell component in a pathogen actually inhibits infection of a mammal by the pathogen."

Claims 56 and 57 have been amended so that there is no need for this step, and so that the result of the claim agrees with the preamble.

Claim 57 is said to be "vague and indefinite in that there is no clear and positive prior antecedent basis for the term 'the control animals' in step (f)."

Proper antecedent basis has been provided by amending step (d) of Claim 57.

Claim 58 is said to be "vague and indefinite in that there is no clear and positive prior antecedent basis for the term 'the control cells' in step (b)."

Claim 58 has been amended so that the term "control cells" is introduced for the first time in step (b) without a definite article, and thus requires no prior antecedent basis in this step.

Claim 58 is also said to be vague and indefinite in that the preamble specifies "A method for identifying a biomolecular inhibitor of infection" while the claim concludes with "the biomolecule is a biomolecular inhibitor of cell growth."

Claim 58 has been amended as the Examiner suggested.

Rejection of Claims 1-6 Under 35 U.S.C. § 102(e)

Claims 1-6 have been rejected under 35 U.S.C. § 102(e), as they are said to be anticipated by Contag *et al.* (US Patent No. 5,650,135).

Contag *et al.* (US 5,650,135) describe vectors and host cells that can produce the enzymes necessary for luciferase synthesis wherein the genes encoding the enzymes can be under the control of constitutive or inducible promoters. Thus, the host cells can produce light. The host cells can be administered to a subject.

Claims 3-5 have been canceled. Claims 1 and 6 have been amended to describe a method to determine whether a biomolecule inhibits infection by a pathogen. Contag *et al.* do not look for an effect of the biomolecule on infection in the animal. Contag *et al.* do not describe a step of a method in which test and control animals are monitored for signs of infection by a pathogen producing (test animals) or not producing (control animals) a biomolecule (for example, luciferase).

Rejection of Claims 1-4 and 6 Under 35 U.S.C. § 102(b)

Claims 1-4 and 6 have been rejected under 35 U.S.C. § 102(b), as they are said to be anticipated by Kernodle *et al.* (*Infection and Immunity 65*(1):179-184, January 1997). Claims 3-5 have been canceled. Claims 1 and 6 have been amended.

Kernodle, D.S. *et al.* describe experiments in which vectors were constructed carrying either the *hla* gene (encoding alpha-toxin of *Staphylococcus aureus*) or a gene encoding antisense *hla* RNA, each gene under the control of the *hla* promoter. The vectors were transformed into *S. aureus*, and the transformants were used to infect mice. The mice infected with the antisense *hla*-containing transformant had a higher survival rate than those infected with the vector carrying the *hla* gene or the parent vector without insertion of any *hla* DNA. The Kernodle *et al.* reference does not describe a step of regulating expression of the gene to produce a biomolecule in the cell after the cell has been introduced into the animal. Therefore, Claims 1, 2 and 6 are not anticipated by the Kernodle reference.

Rejection of Claims 1-6 Under 35 U.S.C. § 102(e)

Claims 1-6 have been rejected under 35 U.S.C. § 102(e), as they are said to be anticipated by Jacobs Jr. *et al.* (US 5,981,182). Claims 3-5 have been canceled. Claims 1 and 6 have been amended.

Jacobs Jr. *et al.* (US 5,981,182) describe vectors with inserted DNA segments the design of which would take advantage of the splicing of the encoded inteins. The vectors may be introduced into host cells. The Jacobs Jr. *et al.* patent does not describe a step of regulating expression of the gene to produce a biomolecule in the cell after the cell has been introduced into an animal. The modes of regulating the expression of the inserted gene pointed out by the Examiner (see column 9, lines 57-60) are not described as being used after the host cell is introduced (by "immunization" -- see column 10, lines 8-13) into an animal. Therefore, Claims 1, 2 and 6 are not anticipated by the Jacobs, Jr. *et al.* patent.

## CONCLUSION

The Examiner is respectfully requested to consider the above amendments and remarks, and to further examine and reconsider the application. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 39, line 13 through page 40, line 7 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Regulated intracellular expression of the Pro-3 peptide in *E. coli* was achieved by fusing an oligonucleotide encoding the peptide to the 5' end of a gene encoding a glutathione S-transferase (GST) protein. To generate the peptide expression construct, the Pro-3/GST fusion gene was PCR amplified using a combination of the Pro3, Pro3/GST, and GST/R primers as illustrated in Figure 1. Primers Pro3 and Pro3/GST encode the Pro-3 peptide sequence; the latter anneals to the 5' end of the GST gene on plasmid pGEX-4T2 (Pharmacia). A 4-amino acid linker was introduced between the Pro-3 peptide and GST for flexibility. The PCR product was further amplified with primers Pro3(Kpn) and GST/R(Bam), digested with KpnI and BamHI restriction endonucleases, and ligated to the KpnI/BamHI sites of the expression vector pPROTet (Clontech, Palo Alto, CA) using standard cloning protocols. pPROTet uses the $P_L$ promoter of phage lambda combined with the Tet operator of the Tn10 tetracycline resistance operon to direct the regulated expression of the cloned gene (Clontech, PROTM Bacterial Expression System User Manual, PT3161-1, Version PR7Y629). The ligated DNA was then used to transform DH5αPRO (Clontech), an *E. coli* strain expressing the Tet repressor. Clone $pC^3844$ was sequenced and identified as containing the Pro-3/GST fusion gene. The linker between the Pro3 peptide and GST is Glu-Gly-Gly-Gly (SEQ ID NO:18). $pC^3844$ was also transformed into the *E. coli* strain JM109/pSC, which is JM109 harboring a plasmid expressing Tet repressor that was isolated from BL21PRO (Clontech). The resulting *E. coli* strain is called JM109/pSC/$pC^3844$.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method for determining whether a biomolecule [produces a phenotypic effect on] inhibits infection by a pathogen cell, comprising the steps of:

a) introducing into [an] a test animal and into a control animal a pathogen cell comprising an exogenous regulable gene encoding the biomolecule;

b) regulating expression of the gene to produce the biomolecule in the cell in the test animal but not in the cell in the control animal; and

c) monitoring said [cell in the animal] test and control animals for [a phenotypic effect] signs of infection;

whereby [a cell which manifests a phenotypic effect] observing fewer or less severe signs of infection in said test animal compared to signs of infection in the control animal indicates that the biomolecule [produced in the cell is a biomolecule that produces a phenotypic effect on] inhibits infection by the pathogen cell.

6. (Amended) A method for determining whether a biomolecule [produces a phenotypic effect on] inhibits infection by a pathogen cell, comprising the steps of:

a) constructing a pathogen cell comprising an exogenous regulable gene encoding the biomolecule;

b) introducing said pathogen cell into [an] a test animal and a control animal;

c) regulating expression of the gene to produce the biomolecule in the pathogen cell in the test animal but not in the cell in the control animal; and

d) monitoring said [cell in the animal] test and control animals for [a phenotypic effect] signs of infection;

whereby [a cell which manifests a phenotypic effect] observing fewer or less severe signs of infection in said test animal compared to signs of infection in the control animal indicates that the biomolecule [produces a phenotypic effect on] inhibits infection by the pathogen cell.

7. (Amended) A method for determining whether a biomolecule is a biomolecular inhibitor of growth of cells, comprising:

a) introducing into one or more test animals and into one or more suitable control animals cells having a regulable gene encoding a biomolecule;

b) regulating, in the test animals, expression of the gene to allow production of the biomolecule; and

c) monitoring said test animals for growth of the cells;

wherein observing fewer of the cells or a slower growth rate of the cells in said test animals compared to the number of the cells or growth rate in suitable control animals indicates that the biomolecule is a biomolecular inhibitor of growth of the cells.

8. (Amended) A method for assessing whether a biomolecule is a biomolecular inhibitor of growth of cells in a host mammal comprising:

a) constructing cells having a regulable gene encoding the biomolecule;

b) introducing the cells into test animals and into suitable control animals;

c) regulating, in the test animals, expression of the regulable gene to produce the biomolecule; and

d) monitoring the test animals and control animals for growth of the cells;

wherein observing less growth of the cells in the test animals than in the control animals indicates that the biomolecule is a biomolecular inhibitor of growth of the cells.

11. (Amended) A method for determining whether a target component of a cell is essential for [normal] growth of said cell, comprising:

a) in cells comprising a biomolecule and a target cell component, wherein the biomolecule is a biomolecular binder of the target cell component, and wherein a gene encoding the biomolecule is regulable, regulating expression of the gene to produce the biomolecule;

b) monitoring growth of the cells in culture relative to growth of suitable control cells, whereby, if growth is decreased in the cells compared to growth of suitable control cells, then the biomolecule is a biomolecular inhibitor of growth <u>of the cells</u>;

c) introducing into one or more test animals cells in which growth can be decreased compared to the control cells as determined in step b);

d) regulating expression of the gene to produce the biomolecular inhibitor of growth in the introduced cells; and

e) monitoring said test animals for inhibition of the growth of the cells;

wherein observing fewer cells or slower growth of cells in said test animals compared to cells or growth of cells, respectively, in suitable control animals indicates that the target component of said cell is essential for [normal] growth of said cell.

23. (Amended) A method for identifying a compound which [produces] <u>is a candidate for producing</u> a phenotypic effect in a cell, said method comprising the steps of:

a) constructing a cell comprising an exogenous regulable gene which encodes a biomolecule;

b) introducing said cell into an animal;

c) regulating expression of the gene to produce the biomolecule in the cell;

d) monitoring said cell in the animal for the phenotypic effect; and

e) identifying, if the biomolecule caused the phenotypic effect, one or more compounds that competitively bind to a target cell component, whereby if the compound competitively binds to the target cell component, then the compound [produces] <u>is a candidate for producing</u> the phenotypic effect.

50. (Amended) A method for [determining whether a biomolecule produces] <u>identifying a compound which is a candidate for producing</u> a phenotypic effect on a first cell, comprising:

a) identifying a biomolecular binder of an isolated target cell component of the first cell;

b) constructing a second cell comprising the target cell component and an exogenous, regulable gene which encodes the biomolecular binder;

c) introducing the second cell into one or more animals;

d) regulating expression of the gene, thereby producing the [biomolecule] biomolecular binder in the second cell;

e) monitoring the second cell in the animal(s) for the phenotypic effect; and

f) identifying, if the biomolecular binder caused the phenotypic effect in the second cell, one or more compounds that compete with the biomolecular binder for binding to the target cell component;

whereby, if a compound competes with the biomolecular binder for binding to the target cell component, then the compound [produces] is a candidate for producing the phenotypic effect on the first cell.

56. (Amended) A method for identifying one or more compounds that bind to a target cell component in a pathogen and [inhibit] are candidates for inhibiting infection of a mammal by the pathogen comprising:

a) constructing a pathogen comprising a regulable gene encoding a biomolecule which binds to the target cell component;

b) infecting one or more test animals with the constructed pathogen, and one or more control animals with the constructed pathogen or with a control pathogen;

c) regulating expression of the regulable gene in the test animals to produce the biomolecule;

d) monitoring the test animals and [one or more suitable] the control animals for signs of infection, wherein observing fewer or less severe signs of infection in the test animals than in the control animals indicates that the biomolecule is a biomolecular inhibitor of infection; and

e) identifying one or more compounds that compete with the biomolecular inhibitor of infection for binding to the target cell component in a competitive binding assay;

whereby, if a compound competes with the biomolecular inhibitor of infection for binding to the target cell component, then the compound [binds] is a candidate for binding to a target

cell component in a pathogen and [inhibits] inhibiting infection of a mammal by the pathogen.

57. (Amended) A method for identifying one or more compounds that [bind] are candidates for binding to a target cell component in a pathogen and [inhibit] inhibiting infection of a mammal by the pathogen, comprising:

a) constructing a pathogen comprising a regulable gene encoding a biomolecule which binds to the target cell component;

b) regulating expression of the gene in a culture of constructed pathogen cells, thereby producing the biomolecule in the constructed pathogen cells;

c) monitoring growth of the constructed pathogen cells in culture, relative to growth of suitable control cells, whereby, if growth is decreased in the constructed pathogen cells, compared to growth of the control cells, then the biomolecule is a biomolecular inhibitor of growth;

d) infecting one or more test animals with the constructed pathogen, and one or more control animals with the constructed pathogen or with a control pathogen;

e) regulating expression of the regulable gene in the test animals, thereby producing the biomolecule;

f) monitoring the test animals and the control animals for signs of infection, wherein observing fewer or less severe signs of infection in the test animals than in the control animals indicates that the biomolecule is a biomolecular inhibitor of infection by the pathogen; and

g) identifying one or more compounds that compete with the biomolecular inhibitor of infection for binding to the target cell component;

whereby, if a compound competes with the biomolecular inhibitor of infection for binding to the target cell component, then the compound [binds] is a candidate for binding to the target cell component in the pathogen and [inhibits] inhibiting infection of the mammal by the pathogen.

58. (Amended) A method for identifying a biomolecular inhibitor of infection by a pathogen, comprising:

a) in pathogen cells comprising a biomolecule and a cell component, wherein the biomolecule is a biomolecular binder of the cell component, and expression of the gene encoding the biomolecule is regulable, regulating expression of the gene, thereby producing the biomolecule;

b) monitoring growth of the pathogen cells in culture relative to growth of [the] control cells, whereby, if growth is decreased in the pathogen cells compared to growth of the control cells, then the biomolecule is a biomolecular inhibitor of growth of the pathogen;

c) infecting one or more test animals and one or more control animals with the pathogen cells in which growth was decreased compared to the control cells in step b);

d) regulating expression of the gene in the test animals, thereby producing the biomolecule; and

e) monitoring said test animals and control animals for signs of infection;

wherein observing fewer or less severe signs of infection in said test animals compared to signs of infection in [suitable] the control animals indicates that the biomolecule is a biomolecular inhibitor of [cell growth] infection by the pathogen.